REMARKS

Claims 38, 40, and 61 are pending in this patent application. No claims have been amended, added, or canceled, herein. Applicant respectfully requests reconsideration of the rejections of record in view of the following remarks.

Alleged Obviousness

Claims 38, 40, and 61 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by published U.S. patent application number 2004/0192626 ("the McSwiggen application") in view of published U.S. patent application number 2003/0166282 ("the Brown application"), and have been independently rejected as allegedly rendered obvious by the McSwiggen application in view of published U.S. patent application number 2005/0181382 ("the Zamore application"). Applicant respectfully requests reconsideration and withdrawal of these rejections because the claimed compositions would not have been obvious to those of ordinary skill in the art at the time of the invention in light of the teachings provided in the cited references.

The claims recite compositions comprising a duplex consisting of an antisense oligonucleotide and a sense oligonucleotide in which the antisense and sense oligonucleotides are complementary to each other and the antisense oligonucleotide is complementary to a target nucleic acid. Each nucleoside of the antisense oligonucleotide comprises a 2'-fluoro modification, each guanine of the sense oligonucleotide is substituted with an inosine, and the sense oligonucleotide comprises at least one inosine.

Because obviousness is necessarily determined as of the time of invention, it is fundamental that the Office avoid using hindsight when assessing obviousness.[1] In this regard, the Supreme Court recently indicated in *KSR Int'l Co. v. Teleflex* that "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[2] To avoid the trap of hindsight, a finding of obviousness therefore requires the

[1] See e.g., *KSR Int'l Co. v. Teleflex*, 127 S.Ct. 1727, (2007) (warning against "the distortion caused by hindsight bias . . . and arguments reliant on *ex post* reasoning."); 35 U.S.C. § 103 (requiring determination of whether an invention "would have been obvious at the time the invention was made.").
[2] *Id.*

Office to identify "a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the [known] elements *in the way the claimed new invention does*."[3] In applying these principles to a case involving chemical compounds, the Federal Circuit held in *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd* that "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."[4] Moreover, according to the Federal Circuit "an invention would not be deemed obvious if all that was suggested 'was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.'"[5]

In the present case, the Office has failed to provide reasons why those of ordinary skill would have combined particular aspects of the cited references to arrive at the claimed compositions. Instead, the Office relies on hindsight to pick and choose elements from the vast, unpredictable, and in some instances contrary, art, to arrive at the claimed subject matter, and the Office has therefore failed to properly establish *prima facie* obviousness. The cited references, in fact, fail to render the claimed compositions obvious, for at least the following reasons.

The McSwiggen application describes siRNA molecules in which the antisense strand is complementary to the RNA of the IKK-gamma or PKR gene.[6] The McSwiggen application includes description of vast genuses of siRNA molecules, and broadly discusses possible chemical modifications for such molecules. In addition to this broad description, the application describes a number of specific, active siRNA molecules, which have chemical modifications that differ from those present in the claimed oligonucleotides. Specifically, the McSwiggen application begins with broad generalized teachings, including description of a vast genus of possible nucleoside modifications. For example, page 9 depicts the structure of the ribose sugar ring of a ribonucleoside in which each position (labeled R3, R4, R5, R6, R7, R8, R10, R11, and R12) may independently be modified with any of a list of possible

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[3] *Id.* (emphasis added).
[4] *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (emphasis added).
[5] *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 83 USPQ 2d 1289, 1305 (Fed. Cir. 2007), (citing *In re O'Farrell*, 853F.2d 894, 903 (Fed. Cir. 1988)).
[6] Col. 5, lines 15 to18.

substituents. Although certain 2'-modifications, including 2'-fluoro, are specifically mentioned, the McSwiggen application also describes countless modifications at every other possible position of the nucleoside. The McSwiggen application also discusses the possible numbers of modified nucleosides and/or modified linkages in an oligonucleotide (e.g., about 1 to about 10 or more).[7] Beyond these general statements that do no more than suggest varying all modifications at all possible positions of an oligonucleoside, the McSwiggen application describes certain specific siRNA molecules. None of the specific molecules, however, comprises complementary antisense and sense oligonucleotides where the antisense oligonucleotide is complementary to a target nucleic acid, each nucleoside of the antisense oligonucleotide comprises a 2'-fluoro modification, each guanine of the sense oligonucleotide is substituted with an inosine, and the sense oligonucleotide comprises at least one inosine, as claimed.

The McSwiggen application also describes some of the goals of chemically modifying siRNA molecules. For example, the McSwiggen application states that chemical modifications may "overcome potential limitations of in vivo stability and bioavailability inherent to native RNA molecules . . . enable a lower dose of a particular nucleic acid molecule for a given therapeutic effect . . . longer half-life in serum . . improving cellular uptake . . . minimize the possibility of activating interferon activity."[8] The McSwiggen application does not suggest more definite solutions to achieve these goals, however. Significantly, the McSwiggen application does not teach how to balance such objectives in designing an siRNA molecule when, for example, a particular modification improves the molecule with respect to one goal, but detracts from it with respect to another goal.

The Office attempts to fill the substantial gaps left by the McSwiggen application by relying on secondary references, including, with respect to the first rejection for alleged obviousness, the Brown application, and with respect to the second rejection for alleged obviousness, the Zamore application. Each of these references fails to compensate for the deficiencies of the McSwiggen application, however.

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[7] See paragraph 67.
[8] See paragraph 12.

The Brown application describes double-stranded RNAs having reduced stability that are said to be useful as small interfering RNAs (siRNAs).[9] The application indicates that a variety of techniques may be used to reduce the stability of siRNA duplexes, including introducing nucleotide analogs into the duplexes, and the application provides a "non-limiting list of possible modifications to be made to the siRNA."[10] Such modifications include introducing one or more phosphorothioate linkages into the siRNA molecules, substituting inosine bases for guanine bases at one or more positions in the siRNA duplexes, substituting 4-thiouridine bases for one or more uracil bases, introducing 4-ethyl cytosine at one or more positions in the siRNA duplexes, substituting "an appropriate number" of nucleotides in the siRNA molecules with 3-nitropyrrole and/or 5-nitroindole nucleotides, introducing one or more abasic sites in the sense strand of the siRNA molecules, and introducing one or more mismatches in the siRNA molecules.[11]

Significantly, nothing in the Brown application would have suggested to those skilled in the art that incorporation of an inosine base would be any more advantageous or desirable than incorporation of any of the other chemical modifications described in the Brown application. Moreover, the Brown application provides no guidance regarding the position or the strand at which the described chemical modifications should be introduced. Furthermore, the Brown application fails to describe introducing 2'-fluoro groups into each nucleoside of the antisense strand of siRNA molecules. The Brown application, when viewed in light of the teachings of the McSwiggen application, therefore would not have rendered obvious the claimed complementary sense and antisense oligonucleotides in which the antisense oligonucleotide comprises 2'-fluoro modified nucleosides and the sense oligonucleotide comprises at least one inosine, because the combined teachings of the references would not have suggested this specific combination of chemical modifications. Rather, the combined teachings indicate that a vast number of different types of chemical modifications can be introduced at every possible position in the two strands of siRNA molecules, resulting a nearly limitless combination of possible chemical modifications that could be introduced into siRNA molecules.

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[9] Paragraphs 18 and 29.
[10] Paragraphs 31 to 38.
[11] *Id.*

The Zamore application in combination with the McSwiggen application similarly would not have rendered the claimed duplexes obvious. The Zamore application describes methods that are said to improve the efficiency of an RNAi reaction that involve modifying an siRNA duplex so that the base pair strength between the 5' end of the antisense strand and the 3' end of the sense strand is lessened relative to the base pair strength between the 5' end of the sense strand and the 3' end of the antisense strand.[12] The application describes numerous and varied means for lessening the strength of the base pair between the 5' end of the antisense strand and the 3' end of the sense strand, including incorporating fewer G:C base pairs between the 5' end of the antisense strand and the 3' end of the sense strand than between the 3' end of the antisense strand and the 5' end of the sense strand; introducing a mismatched base pair, preferably a G:A, C:A, C:U, G:G, A:A, C:C, or U:U base pair, between the 5' end of the antisense strand and the 3' end of the sense strand; introducing a wobble base pair, such as a G:U base pair, between the 5' end of the antisense strand and the 3' end of the sense strand; introducing a rare nucleotide, such as inosine, 1-methyl inosine, pseudouridine, 5,6-dihydrouridine, ribothymidine, 2N-mtehylguanosine, or ^{2,2}N,N-dimethylguanosine, at the 5' end of the antisense strand or the 3' end of the sense strand; and introducing a base pair comprising a modified nucleotide, such as 2-amino-G, 2-amino-A, 2,6-diamino-G, or 2,6,-diamino-A, between the 5' end of the antisense strand and the 3' end of the sense strand.[13] Significantly, the Zamore application does not teach that incorporating an inosine base into an siRNA molecule would be any more advantageous or desirable than utilizing any of the other means described in the application for lessening base pair strength.

Moreover, the Zamore application fails to describe or suggest introducing 2'-fluoro modified nucleosides at each position of the antisense strand of a duplex of complementary sense and antisense oligonucleotides. Instead, while indicating that the RNA strands of siRNA molecules may contain modified nucleosides, the Zamore application provides no specific guidance regarding the number and placement of such modified nucleosides within siRNA duplexes, with the exception of indicating that placement at the ends of the RNA strands is preferred. In this regard, the Zamore application states that chemical modifications should occur "at positions where the target-specific activity, e.g., the RNAi mediating activity

[12] Paragraph 37.
[13] Paragraphs 43-47 and 59.

is not substantially effected [*sic*], e.g., in a region at the 5'-end and/or the 3'-end of the RNA molecule. Particularly, the ends may be stabilized by incorporating modified nucleotide analogues."[14] The combined teachings of the Zamore and McSwiggen applications therefore fail to describe or suggest compositions comprising complementary sense and antisense oligonucleotides wherein one sense oligonucleotide comprises an inosine base and the antisense oligonucleotide comprises 2'-fluoro modified nucleosides at each position of the oligonucleotide, as claimed.

Significantly, the Office offers no reason why those of ordinary skill in the art would have selected the *particular* chemical modifications recited in the present claims before applicant's invention from among the nearly limitless number of possible combinations of modifications described in the art in order to design and produce the claimed compositions, particularly in light of the limited guidance provided in the cited references regarding the specific type, number, and positioning of chemical modifications that would confer advantageous properties to oligomeric compounds bearing the modifications. The cited references thus fail to describe or suggest the claimed compositions comprising a duplex consisting of complementary antisense and sense oligonucleotides where the antisense oligonucleotide is complementary to a target nucleic acid, each nucleoside of the antisense oligonucleotide comprises a 2'-fluoro modification, each guanine of the sense oligonucleotide is substituted with an inosine, and the sense oligonucleotide comprises at least one inosine.

Moreover, the art of siRNA design at the time of the invention was unpredictable. Since those of ordinary skill could not have anticipated which chemical modifications in siRNA duplexes would have resulted in active compounds, the invention represents a selection from among a vast number of unpredictable possible choices and is therefore non-obvious. It appears that the Office's approach to designing siRNA molecules in view of the vast teaching in the art regarding chemical modification of nucleosides would be to simply try all possible combinations of modifications. Not only is such an approach impossible, given the vast number of combinations of modifications, it also fails to support an

[14] Paragraph 91.

obviousness rejection because the art does not support a finding that the claims represent a selection from among predictable possibilities.

In this regard, in *KSR*, the Supreme Court noted that when "there are a *finite* number of identified *predictable* solutions a person of ordinary skill has good reason to pursue the known options in his or her technical grasp."[15] *KSR* involved simple technology with only a few variables; a control pedal and an electronic throttle, each of which was separately known in the art. In *Takeda*, though, the inventors selected a lead compound from among several hundred for modification and further investigation. In finding non-obviousness, the *Takeda* Court contrasted this situation from that in *KSR*, remarking that, "[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation."[16] Similarly, the invention in *Ortho McNeil Pharmaceuticals v. Mylan Laboratories,* an epilepsy drug, did "not present a finite (and small in the context of the art) number of options easily traversed to show obviousness."[17]

In *KSR*, once the claimed control pedal was designed, there was little doubt that it would work for its intended purpose. Thus, as the Court noted, the invention was selected from among "predictable solutions." In *Takeda*, though, the lead compound (as discussed above, selected from several hundred) was modified in two ways with unpredictable results. To arrive at the claimed compound from the identified lead, a methyl group was homologated, and the resulting ethyl group was moved from one position on a ring to another. Although these modifications are easily and routinely made by skilled chemists, the court found nothing in the art to predict that "performing the specific steps of replacing the methyl group of the 6-methyl compound with an ethyl group, and moving that substituent to the 5-postion of the ring, would have provided a broad safety margin."[18] Until the compound was made and tested, its properties could not have been predicted. Similarly, the invention in *Sanofi-Synthelabo v. Apotex* was an isolated enantiomer of a known racemate, about which an expert testified that "no known scientific principle allows prediction of the degree

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[15] *KSR* at 1742 (emphasis added).
[16] *Takeda* at 1359.
[17] 520 F.3d 1358, 1364 (Fed. Cir. 2008).
[18] *Id.*

to which stereoisomers will exhibit different levels of therapeutic activity and toxicity."[19] Accordingly, the Federal Circuit upheld a finding of non-obviousness, noting that "a person of ordinary skill in this field would not reasonably have predicted that the dextrorotory enantiomer would provide all of the antiplatelet activity and none of the adverse neurotoxicty."[20]

The issue in the present case is thus whether the selected combination of modifications utilized in the claimed compositions would have been predictable (like the simple electronic control throttle in *KSR*) or unpredictable (like the chemical modifications in *Takeda* or the enantiomers in *Sanofi-Synthlabo*). The Office offers no *specific* reasons why those skilled in the art would have reasonably expected before applicant's invention that the claimed selection of modifications present in each of the strands of an siRNA duplex would have yielded active siRNA compounds. Instead, the Office offers only the conclusory statement that the claimed references "provide motivation and a reasonable expectation of success in including inosine nucleotides in a siRNA."[21] The Office does not support this assertion with specific evidence or reasoning, however. For example, the Office offers nothing specific to support the notion that siRNA duplexes bearing the chemical modifications recited in the claims would have been reasonably expected to reduce target mRNA before applicant's invention, in light of the highly unpredictable state of the art, similar to the situation at issue in *Takeda*.

The Office further asserts that the chemical modifications present in the claimed oligomeric compounds represents nothing more than "design choice" made in the course of "routine optimization."[22] According to the Office's reasoning, the compound at issue in *Takeda* would also have been obvious because its production was merely a matter of design choice made during routine optimization of a known compound. As made clear by the Federal Circuit in *Takeda*, however, far more than an unsupported assertion of obviousness based upon structural similarity is required to properly establish obviousness where the art is unpredictable. The situation in *Takeda* mirrors that of the presently claimed oligomeric compounds, in light of the upredictability in the art of siRNA design and production.

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[19] 550 F.3d 1075, 1087 (Fed. Cir. 2008 .
[20] *Id.*
[21] Office action dated April 1, 2009, page 7.
[22] *Id.* at page 5.

The Office dismisses the complexity of siRNA design by simply remarking that certain modifications can provide desirable properties and apparently concluding that all modifications therefore would have been obvious. Omitted from that conclusion is the complicated, unpredictable reality that improving any one property may reduce or abolish another property. For example, if one were to adopt the reasoning set forth by the Office, oligomeric compounds modified at every position with 2'-O-methyl groups would have been expected to have desirable resistance to nucleases and to have high affinity for target messenger RNA, when utilized in siRNA molecules. The art reports, however, that such compounds are totally inactive in RNAi, making them unsuitable as siRNA molecules.[23] Many variables influence whether siRNA molecules bearing particular chemical modifications will be active. In the setting of such unpredictability, the Office provides no reasonable basis for selecting the particular modifications recited in the present claims. The Office glosses over this complexity, blithely labeling it "routine optimization." In reality, balancing competing properties has proven to be unpredictable and extremely challenging.

When one considers the state of the art on balance, it becomes clear that the modifications described in the cited references are neither universally beneficial nor detrimental. Rather, the art teaches that modifications may provide benefits or detriments depending upon their particular number and placement within an oligonucleotide. As in *Takdea* and *Sanofi*, at the time of filing, there was no known scientific principle to allow prediction of which chemical modifications would yield active compounds and which would not. Such level of unpredictability in the art is incompatible with finding the claimed oligonucleotides obvious.

In light of the unpredictability in the art at the time of the invention, and the fact that the Office has failed to provide credible reasons why those skilled in the art would have designed and produced oligomeric compound bearing the particular claimed chemical modifications before applicant's invention, compositions comprising the compounds would not have been obvious at that time. Applicant accordingly, respectfully, requests withdrawal of the rejection.

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[23] Elbashir *et al.*, *EMBO Journal*, 2001, 20, 6877-6888.

Conclusion

Applicant believes that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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